



IMPACT OF THE RS9939609 POLYMORPHISM OF THE FTO GENE ON OBESITY IN A BRAZILIAN POPULATION

IMPACTO DO POLIMORFISMO RS9939609 DO GENE FTO NA OBESIDADE EM UMA POPULAÇÃO BRASILEIRA

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ABSTRACT: The objective of this study was to investigate the association between the rs9939609 polymorphism of the FTO gene and obesity in individuals from the Greater Vitória region, Espírito Santo, Brazil. This was a cross-sectional study involving 47 participants in whom anthropometric measurements were assessed, including body mass index (BMI), waist circumference, and waist-to-height ratio. Genomic DNA was extracted using the Salting Out method, and the rs9939609 polymorphism was genotyped by real-time PCR. Participants with BMI > 25 presented significantly higher anthropometric measurements ($p < 0.0001$); however, there was no difference in the genotypic distribution of rs9939609 between groups ($p = 0.5522$), nor was there an association between genotypes and anthropometric parameters ($p > 0.05$). The rs9939609 polymorphism of the FTO gene showed no significant association with obesity, suggesting the influence of other genetic and environmental factors, and studies with larger sample sizes and analyses of gene-environment interactions are recommended.

KEYWORDS: Adiposity. Anthropometry. Genetic predisposition. rs9939609 polymorphism.

RESUMO: O objetivo foi investigar a associação entre o polimorfismo rs9939609 do gene *FTO* e a obesidade em indivíduos da Grande Vitória, Espírito Santo, Brasil. Estudo transversal com 47 participantes, nos quais foram avaliadas medidas antropométricas (IMC, circunferência da cintura e razão cintura-altura). O DNA genômico foi extraído pelo método Salting Out e o polimorfismo rs9939609 foi genotipado por PCR em tempo real. Participantes com IMC > 25 apresentaram medidas antropométricas significativamente maiores ($p < 0,0001$). No entanto, não houve diferença na distribuição genotípica do rs9939609 entre os grupos ($p = 0,5522$), nem associação entre genótipos e parâmetros antropométricos ($p > 0,05$). O polimorfismo rs9939609 do *FTO* não apresentou associação significativa com a obesidade, sugerindo a influência de outros fatores genéticos e ambientais. Estudos com amostras maiores e análise de interações gene-ambiente são recomendados.

PALAVRAS-CHAVE: Adiposidade. Antropometria. Predisposição genética. Polimorfismo rs9939609.

INTRODUCTION

Obesity is a chronic, multifactorial condition and a public health challenge worldwide, with significant economic, social, and health implications, particularly in developing countries such as Brazil^{1,2,3}. The global prevalence of overweight and obesity in adults was estimated in approximately 45% in 2021⁴. However, these rates vary across regions: in the United States, obesity affects approximately 40% of adults⁵, while European countries report an average prevalence of around 16%⁶. In Asia, obesity trends are rising rapidly, particularly in urban populations, where dietary patterns and physical activity levels have shifted significantly⁷.

Obesity prevalence in Brazil rose from 11.8% in 2006 to 20.3% in 2019 and is expected to reach 29.6% by 2030, with significant disparities across regions and sociodemographic groups⁸. This condition is a major risk factor for non-communicable chronic diseases, including type 2 diabetes, hypertension, cardiovascular diseases, and certain types of cancer^{9,10}. Given its impact on morbidity and mortality, prevention and health promotion strategies are essential to mitigate its burden, making its management a priority for public health policies^{2,11,12}.

Obesity is characterized by the excessive body fat accumulation and is commonly assessed using the Body Mass Index (BMI)¹². Individuals with a BMI over or equal to 30 kg/m² are classified as obese, while those with a BMI between 25 and 29.9 kg/m² are considered overweight^{12,13}. The World Health Organization (WHO) emphasizes the importance of preventive measures such as improving dietary patterns, increasing physical inactivity, and implementing public policies that restrict the availability of ultra-processed foods^{13,14}.

While lifestyle factors are well-established contributors to obesity, genetic predisposition also plays a significant role. The interaction between genetic factors and environmental influences is a crucial area of study for advancing personalized prevention strategies¹³. Among the genetic markers associated with obesity, polymorphisms in the fat mass and obesity-associated (FTO) gene have been extensively investigated^{15,16}. The rs9939609 polymorphism in FTO is associated with an increased risk of obesity, particularly in individuals homozygous for the A allele, who exhibit a greater tendency for weight gain^{17,18,19}. Studies conducted in European^{17,18}, Asian^{19,20}, and North American²¹ populations have demonstrated varying degrees of association between FTO polymorphisms and obesity, suggesting that genetic background and environmental factors may influence these associations. However, research on genetically diverse populations, such as those in Latin America, remains limited.

The emerging field of nutrigenomics focuses on the interaction between genetic and environmental factors, investigating how dietary components influence the expression of genes involved in fat metabolism and appetite regulation^{22,23,24}. Understanding these interactions is fundamental for health promotion initiatives that emphasize early interventions and personalized nutritional strategies. Given the rising prevalence of obesity and the genetic diversity of the Brazilian population^{8,26}, understanding the association between genetic polymorphisms, such as SNP rs9939609 in the FTO gene, and obesity is critical. While studies in Western countries have provided important insights into this relationship^{17,18,21} further research is needed in Latin American populations to determine whether similar genetic association hold true and to explore potential interactions with regional dietary and lifestyle factors.

Therefore, this study investigates the relationship between SNP rs9939609 and obesity in a sample from the Vitória metro area, Espírito Santo, Brazil. By focusing on a population with unique genetic and environmental characteristics, the research aims to provide valuable insights into the genetic factors contributing to obesity in Brazil. The findings could help guide more effective and personalized

prevention and health promotion strategies, contributing to the reduction of obesity-related diseases and improving public health outcomes.

METHODOLOGY

PARTICIPANTS

This cross-sectional study was carried out in the Southeast region of Brazil, specifically in the State of Espírito Santo, from August to December 2023. A total of 47 genetic material samples were collected from male and female participants selected by convenience in three locations within the Vitória metro area, which includes seven districts. The inclusion criteria were individuals over the age of 18, participants with a BMI within the eutrophic category (BMI between 18.5 and 24.9) or in the overweight/obesity range (BMI above 25.0), and those who signed the Informed Consent Form. The exclusion criteria included individuals with a BMI below 18.5, as well as participants with severe comorbidities, such as severe cardiovascular diseases or type 1 diabetes, which could interfere with the interpretation of the results. Additionally, individuals using medications that alter metabolism, such as drugs for obesity or endocrine diseases, were excluded, except for those with controlled type 2 diabetes and no complications. A known family history of genetic diseases that could influence weight metabolism, such as Prader-Willi syndrome or rare genetic disorders, was also an exclusion criterion. These criteria were established to minimize selection bias and ensure that the sample accurately represented the study population, limiting the impact of external factors that could confound the results related to the rs9939609 polymorphism. This study was approved by the Research Ethics Committee of Vila Velha University, under protocol number 6.202.891.

SAMPLES COLLECTION

The anthropometric assessment of the participants included the body mass index (BMI), which was obtained through weight and height values. In addition to measuring the waist circumference (WC), the waist-to-height ratio (WHtR) was calculated. These parameters were collected by a single evaluator with prior experience. Furthermore, the presence of comorbidities was assessed through a questionnaire.

Genetic material samples were collected using methods such as blood collection in ethylenediaminetetraacetic acid (EDTA), dried blood spot on Flinders Technology Associates (FTA) cards, saliva, or buccal swabs in the Tommasi Laboratory. After the sample collection, DNA extraction was performed in the Molecular Biology area of Tommasi Laboratory, using the Salting Out method adapted from Miller (1988), which simplifies protein removal through dehydration and precipitation of cellular proteins.

For saliva and blood samples, they were added to 1.5 mL tubes along with 600 µL of the SLR 1X buffer solution. The samples were vortexed for 15 seconds and centrifuged for 3 minutes at 3,000 rpm. The supernatant was discarded, completing the lysis of the red blood cells. Then, 500 µL of SLB buffer solution and 20 µL of Proteinase K were added, and the samples were incubated at 56°C for 10 minutes. After incubation, 200 µL of sodium chloride (NaCl) was added, and the samples were centrifuged again for 3 minutes at 7,000 rpm. The supernatants were transferred to new tubes containing 500 µL of isopropyl alcohol and homogenized by inversion. The samples were then centrifuged for 3 minutes at 7,000 rpm.

The supernatant was discarded, and the resulting pellet was washed with 400 μ L of 70% ethanol, followed by centrifugation for 5 minutes at 14,000 rpm. The ethanol was discarded, and the DNA was left to dry at room temperature for 24 hours. Subsequently, the DNA was resuspended in 15 μ L for saliva and 20 μ L for blood, and quantified using the Qubit 2.0 fluorometer (Invitrogen), which provides precise and specific DNA quantification.

The Real-Time Polymerase Chain Reaction (PCR) methodology was used to amplify the genetic material, utilizing MGB probes from the TaqMan® Genotyping Assays (validated kits, biologically informative for the detection of human SNPs), to analyze the FTO gene at the rs9939609 polymorphism site. The AA, AT, and TT genotypes were validated through next-generation sequencing (NGS) to ensure the accuracy of the results.

The PCR process consisted of three main steps. In the first step, denaturation, the temperature was raised to about 96°C, causing the DNA strands to separate. Next, during the annealing step, the temperature ranged from 58°C to 65°C, allowing the specific primers to bind to the target sequence. Finally, in the extension step, the polymerase enzyme added complementary nucleotides to the target DNA sequence at around 72°C. At the end of the experiment, the results were analyzed based on genetic controls to differentiate the AA, AT, and TT genotypes.

STATISTICAL ANALYSIS

Normality of continuous variables was tested by Shapiro Wilk test. All continuous parameters had a non-normal distribution. Continuous variables were presented as media and standard deviation (SD). Categorical variables were presented as number and percentages. Differences between the BMI < 25 and BMI > 25 groups were evaluated using Mann–Whitney (quantitative parameters) or Chi-square tests (qualitative parameters). The relationship between the genotypes of the rs9939609 polymorphism and BMI was tested using the Chi-square test. The relation between anthropometric parameters and FTO rs9939609 genotypes was evaluated with Kruskal-Wallis test followed by Tukey's multiple comparisons test. Data were analyzed using GraphPad Prism® 8.0 software (GraphPad Software, CA, EUA) and analyses were considered statistically significant when $p < 0.05$.

RESULTS

The characteristics of study population were evaluated for a total of 47 individuals, divided into two groups based on BMI: BMI < 25 ($n = 20$) and BMI > 25 ($n = 27$) (Table 1). No statistically significant difference was observed in the mean age between the group ($p = 0.1784$). Regarding gender distribution, there was also no significant difference between the groups ($p = 0.5338$), with a predominance of females in both groups (85.0% in the BMI < 25 group and 77.7% in the BMI > 25 group).

The findings shown significant differences in anthropometric parameters associated with increased BMI (Table 1). BMI values were notably higher in the BMI > 25 group compared to the BMI < 25 group, with a statistically significant difference ($p < 0.0001$). Similarly, WC and WHtR were significantly elevated in individuals with BMI > 25. The BMI > 25 group had a mean WC of 100.6 ± 18.7 cm, compared to 76.7 ± 4.8 cm in the BMI < 25 group ($p < 0.0001$). The WHtR followed a similar pattern, with values of 59.4 ± 10.5 in the BMI > 25 group and 46.0 ± 3.0 in the BMI < 25 group ($p < 0.0001$).

Table 1. Anthropometric parameters of study population.

Parameters	Total	BMI < 25	BMI > 25	<i>p-value</i>
Age (years)	43.8 ± 15.4	40.9 ± 17.3	45.9 ± 13.7	0.1784
Gender				
Male	9 (19.14%)	3 (15.0%)	6 (22.3%)	0,5338
Female	38 (80.86%)	17 (85.0%)	21 (77.7%)	
Weigth (Kg)	82.5 ± 25,2	62.3 ± 8.3	97.5 ± 23.0	<0.0001
Height (m)	1.69 ± 0.08	1.66 ± 0.07	1.69 ± 0.07	0.2258
BMI (Kg/m2)	29.0 ± 8.4	22.3 ± 1.5	34.0 ± 8.0	<0,0001
WC (cm)	92.3 ± 17.1	76.7 ± 4.8	100.6 ± 18.7	<0,0001
WHtR	53.7 ± 10.5	46.0 ± 3.0	59.4 ± 10.5	<0,0001

Data are presented as media ± SD for continuous variables and n (%) for categorical variables. Data were analyzed by Mann-Whitney Test (for non-normally distributed variables), or Chi-square test (for categorical variables). *p*-value for difference between BMI < 25 and BMI > 25 groups. BMI: Body Mass Index; WC: waist circumference; WHR: waist-to-height ratio.

The table 2 shows the genotype distribution of the FTO rs9939609 polymorphism in the BMI groups. Among the individuals with BMI < 25, the genotypes were distributed as follows: TT (35.0%), AT (60.0%), and AA (5.0%). Similarly, for the BMI > 25 group, the distribution was TT (33.4%), AT (51.8%), and AA (14.8%). When comparing the groups, no statistically significant difference in genotype distribution was observed (*p* = 0.5522). In the overall population, the most frequent genotype was AT (55.3%), followed by TT (34.1%) and AA (10.6%). These findings indicate that the FTO rs9939609 polymorphism genotype distribution does not differ significantly between individuals with BMI < 25 and BMI > 25.

Table 2. Genotype distribution of the FTO rs9939609 polymorphism.

FTO rs9939609	BMI < 25	BMI > 25	Total	<i>p-value</i>
TT	7 (35.0%)	9 (33.4%)	16 (34.1%)	0.5522
AT	12 (60.0%)	14 (51.8%)	26 (55.3%)	
AA	1 (5.0%)	4 (14.8%)	5 (10.6%)	
Total	20	27	47	

Data are presented as n (%). Data were analyzed by Chi-square test. *p*-value for difference between BMI < 25 and BMI > 25 groups.

Anthropometric parameters were compared among individuals with different FTO rs9939609 genotypes (Table 3). The mean weight was highest in individuals with the TT genotype, followed by those with the AA genotype and AT genotype. However, the differences were not statistically significant (*p* = 0.497). Likewise, BMI did not differ significantly between the groups (*p* = 0.348). The WC and WHtR also showed no significant differences among the genotypes (*p* = 0.708 and *p* = 0.6244, respectively). These results suggest that the FTO rs9939609 genotypes are not significantly associated with differences in anthropometric parameters in this population.

Table 3. Relation between anthropometric parameters and FTO rs9939609 genotypes.

Parameters	Genotypes			<i>p-value</i>
	TT	AT	AA	
Weigth (Kg)	88.6 ± 32.7	79.0 ± 20.0	81.4 ± 23.4	0.7587
Height (m)	1.67 ± 0.07	1.69 ± 0.07	1.65 ± 0.08	0.5550
BMI (Kg/m2)	31.4 ± 11.3	27.5 ± 6.3	29.4 ± 6.6	0.5900
WC (cm)	93.5 ± 23.9	88.6 ± 15.4	90.0 ± 13.0	0.8544
WHtR	55.7 ± 13.7	55.4 ± 9.0	54.4 ± 6.2	0.6232

Data are presented as media ± SD. Data were analyzed by Kruskal-Wallis test followed by Tukey's multiple comparisons test. BMI: Body Mass Index; WC: waist circumference; WHtR: waist-to-height ratio.

DISCUSSION

Obesity remains a global public health challenge influenced by the interplay between genetic predisposition and environmental factors^{13,14,16}. This study aimed to explore the association between the risk allele (allele A) of the rs9939609 polymorphism in the *FTO* gene and anthropometric measures such as BMI, body weight, and waist circumference, in a Brazilian sample. Contrary to expectations, our results showed no significant association between this polymorphism and the studied variables, even in participants homozygous for the risk allele (AA). These findings highlight the complexity of obesity etiology, where environmental and epigenetic factors might outweigh genetic predisposition in certain populations.

Our results are consistent with previous research conducted in diverse populations, which also reported no associations between the *FTO* gene polymorphism and obesity^{26,27,28,29}. For instance, studies in the Turkish population²⁷ and Chinese cohorts²⁶ suggested that genetic diversity and low-risk allele frequency, respectively, could contribute to the absence of a significant association. Similarly, Brazilian studies by Rodrigues et al.³⁰ and Pereira et al.²⁹ replicated these findings, attributing the discrepancies to the genetic admixture characteristic of Brazil, which may dilute the impact of specific alleles on phenotypic traits such as BMI and waist circumference.

Interestingly, while our findings align with these reports, they contrast with those from Iran by Mehrdad et al.¹⁹, who found a significant association between the A allele and both general and central obesity in a larger sample. Notably, the proportion of homozygous AA individuals in Mehrdad et al.'s study (19%) was comparable to ours (18.5%), suggesting that sample size and environmental variability might explain the differences. These conflicting results underscore the importance of considering population-specific factors, such as genetic background, environmental influences, and sample characteristics, when interpreting the role of the *FTO* gene in obesity.

One remarkable observation in our study was the significantly larger waist circumference in participants with BMI ≥ 25 , reinforcing the relevance of central obesity in metabolic risk assessment. This finding aligns with broader evidence emphasizing the contribution of abdominal adiposity to cardiometabolic risks and highlights the need to account for phenotypic variations in studies of obesity-related genes.

The absence of a significant association in our study suggests that environmental factors may exert a greater influence on weight gain than the rs9939609 polymorphism alone. This aligns with a growing body of literature emphasizing the gene-environment interaction in obesity. Epigenetic mechanisms, such as DNA methylation, may modulate *FTO* gene expression, potentially mitigating the impact of the risk allele³⁰. For instance, nutritional interventions and physical activity have been shown to influence gene expression^{31,32}. Sonestedt et al.³² reported that carriers of the A allele respond better to calorie-reduced diets with increased protein intake, while Danaher et al.³³ demonstrated that high-intensity exercise reduces *FTO* mRNA expression. These findings suggest that lifestyle modifications can override genetic susceptibility, offering practical pathways to obesity management.

However, this study has limitations that justify its consideration. The small sample size, reduced further by technical issues during PCR, limits the statistical power and generalizability of our findings. Additionally, the predominance of female participants may have introduced a sex bias, as hormonal and metabolic differences can influence obesity phenotypes. Future studies should prioritize larger, balanced samples across sexes and regions, which would allow for more nuanced assessments of genetic and environmental interactions.

Although our study did not find a significant association between the rs9939609 polymorphism in the *FTO* gene and obesity-related anthropometric measures, the results highlight the importance of

lifestyle interventions as primary tools for obesity prevention, regardless of genetic predisposition. Evidence that dietary modifications and physical activity can modulate gene expression^{34,35} suggests that personalized interventions based on an individual's metabolic and environmental profile may be more effective than strategies solely focused on genetic risk factors. Furthermore, these findings support the integration of nutrigenomic approaches into health promotion policies. As seen in previous studies, individuals with the A allele may respond differently to dietary interventions^{36,37}. Thus, personalized nutritional counseling that considers both genetic history and dietary habits, can improve the effectiveness of weight management programs. Therefore, our findings suggest that future research should expand on gene-environment interactions in obesity, particularly in diverse populations such as Brazil.

CONCLUSION

In conclusion, while our findings do not support a significant association between the rs9939609 polymorphism and obesity in a Brazilian sample, they underscore the primacy of environmental factors in modulating genetic risk. These results highlight the importance of integrating genetic, environmental, and epigenetic perspectives in obesity research. Further investigation is needed to unravel the population-specific nuances of *FTO* gene function and its interaction with lifestyle factors, contributing to personalized strategies for obesity prevention and management.

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